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Overview: What is Chronic Fatigue Syndrome?

12-12-2003 - **How do you know if you have CFS?**

Diagnosis of CFS is complicated by the fact that fatigue is the single most commonly reported complaint but fatigue is a feature of countless other conditions as well. Because of this, a doctor's first goal is to rule out other illnesses.

The Centers for Disease Control (CDC) has established certain criteria for diagnosing CFS:

1. Fatigue that is persistent, relapsing or debilitating; does not improve with bed rest; and reduces or impairs average daily activity level by more than 50 percent for a period of at least 6 months. Patient has no previous history of fatigue.

2. The patient has 4 or more of the following symptoms, which must have persisted or recurred during 6 or more consecutive months and predated the fatigue:

- Short-term memory or concentration problems
- Sore throat
- Multi-joint pain without joint swelling or redness
- Muscle pain
- Headaches of a new type, pattern or severity
- Non-refreshing sleep
- Post-exertional malaise lasting more than 24 hours

In addition, a number of minor symptoms may also appear:

- Poor sleep
- Achiness
- Brain fog
- Increased thirst
- Bowel disorders

- Recurrent infections
- Exhausting after minimal exertion

The CDC criteria should not be thought of as final guidelines in diagnosing CFS. Research has shown the people with disabling fatigue who fit the CFS criteria have the same immunologic changes and responses to treatment as those who don't fit the criteria.

According to Edward J. Conley, D.O, author of America Exhausted, "At least 50 percent of the patients we see for CFS do not have symptoms severe enough to be classified as CFS, but that does not mean these people are healthy. They just don't fit a committee's definition for CFS."

"My experience also suggests that the underlying causes and the response to treatment are not affected by whether patients strictly meet CDC guides," says Jacob Teitelbaum, M.D. "I prefer to use the term Severe Chronic Fatigue States (SCFS) for these conditions."

In his book, *From Fatigued to Fantastic*, Dr. Jacob Teitelbaum states that it is important to look for and treat all of the factors simultaneously. Chronic Fatigue states are unusual in that each problem can trigger other problems. Because of this, it is rare to find only one single underlying problem by the time the patient seeks medical help.

The process that occurs is analogous to an automobile with no battery and no starter. If you fix only the battery or the starter, the car won't run. If both the battery and the starter are fixed at the same time, the care would be fine. In the same way, if we treat all of a patient's problems simultaneously, the person feels well.

Who Gets CFS?

CFS was once stereotyped as a new "yuppie flu" because those who sought help for and caused scientific interest in CFS in the early 1980s were mainly well-educated, well-off women in their thirties and forties. Similar illnesses, known by different names, however, date back at least to the late 1800s. The modern stereotype arose. Since then, doctors have seen the syndrome in people of all ages, races, and social and economic classes from several countries around the world.

Still, CFS is diagnosed two to four times more often in women than in men, possibly because of

biological, psychological, and social influences. For example, CFS may have a gender difference similar to diseases such as systemic lupus erythematosus and multiple sclerosis, which affect more women than men.

Women may be more likely than men to talk with their doctors about CFS-like symptoms. Some members of the medical community and the public do not know about or are skeptical of the syndrome.

An increasingly diverse patient group will likely emerge as more doctors see CFS as a real disorder.

How Many People Have It?

Because there is no specific laboratory test or clinical sign for CFS, no one knows how many people this illness affects. CDC estimates, however, that as many as 500,000 people in the United States have a CFS-like condition.

What Causes CFS?

While no one knows what causes CFS, for more than a century, doctors have reported seeing illnesses similar to it. In the l860s, Dr. George Beard named the syndrome neurasthenia because he thought it was a nervous disorder with weakness and fatigue. Since then, health experts have suggested other explanations for this baffling illness.

Iron-poor blood (anemia)

Low blood sugar (hypoglycemia)

Environmental allergy

A body wide yeast infection (candidiasis)

In the mid-1980s, the illness became labeled "chronic EBV" when laboratory clues led scientists to wonder whether the Epstein-Barr virus (EBV) might be causing this group of symptoms. New evidence soon cast doubt on the theory that EBV could be the only thing causing CFS. High levels of EBV antibodies (disease-fighting proteins) have now been found in some healthy people as well as in some people with CFS. Likewise, some people who don't have EBV antibodies, and who thus have never been infected with the virus, can show CFS symptoms.

How is CFS Diagnosed?

Doctors find it difficult to diagnose CFS because it

has the same symptoms as many other diseases. When talking with and examining you, your doctor must first rule out diseases that look similar, such as multiple sclerosis and systemic lupus erythematosus in which symptoms can take years to develop. In follow-up visits, you and your doctor need to be alert to any new cues or symptoms that might show that the problem is something other than CFS.

When other diseases are ruled out and if your illness meets other criteria as well, your doctor can diagnose you with CFS (see The CFS Case Definition).

EDITOR'S NOTE: The following information, "Diagnostic Criteria" and "Possible Causes" is from the Life Extension Foundation (LEF) website and was updated in March 2003.

DIAGNOSTIC CRITERIA

CDC Criteria

Oxford Criteria

Additional Symptoms

Laboratory Tests

The criteria for diagnosing CFS were officially defined by the CDC in 1988 and revised in 2001 (CDC 2001). The Oxford criteria differ slightly. The British criteria insist upon the presence of mental fatigue, although the American criteria include a requirement for several physical symptoms, reflecting the belief that CFS has an underlying immune or infectious pathology (Fauci et al. 1998; Reid et al. 2000).

Centers for Disease Control's Criteria for Chronic Fatigue Syndrome
Clinically evaluated, unexplained, persistent, or relapsing fatigue that is:

- Of new or definite onset
- Not a result of ongoing exertion
- Not alleviated by rest
- Results in a substantial reduction in previous levels of occupational, social, or personal activity

Four or more of the following symptoms that persist or recur during 6 or more consecutive months of illness and that do not predate the fatigue.

- Self-reported impairment of short-term memory

or concentration
- Sore throat
- Tender lymph nodes
- Muscle pain
- Multijoint pain without swelling or redness
- Headaches of a new type, pattern, or severity
- Unrefreshing and/or interrupted sleep
- Postexertion malaise (a feeling of general discomfort or uneasiness) lasting more than 24 hours

Exclusion criteria:

- Active, unresolved or suspected disease that is likely to cause fatigue
- Psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)
- Psychotic disorders
- Dementia
- Anorexia or bulimia nervosa
- Alcohol or other substance misuse
- Severe obesity

Oxford (British) Criteria for Chronic Fatigue Syndrome
Severe disabling fatigue of at least a 6-month duration that:

- Affects both physical and mental functioning
- Is present for more than 50% of the time
- Other symptoms, particularly myalgia and sleep and mood disturbances, may be present.

Exclusion criteria:

- Active, unresolved, or suspected disease that is likely to cause fatigue
- Psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)
- Psychotic disorders
- Dementia
- Anorexia or bulimia nervosa

Additional Symptoms

Although the symptoms heretofore listed are the official diagnostic criteria, many patients with CFS present a variety of other symptoms, including:

- Pain (almost universal in chronic fatigue)
- Allergies
- Chemical sensitivities
- Secondary infections, including Candida and viral infections
- Cognitive impairment, including short-term

memory loss, difficulty concentrating and doing word searches and math problems
- Digestive disturbances, such as chronic constipation or diarrhea
- Night sweats or spontaneous daytime sweats, unaccompanied by fever
- Headaches, migraines
- Weakness (paresis), muscle fatigue, and pain (fibromyalgia)
- Premenstrual syndrome (PMS)
- Sleep disorders, including excessive sleep (hypersomnia), light sleep, or an inability to sleep for more than an hour (hyposomnia), disturbing nightmares
- A period of 1-3 hours after awakening during which patients are too exhausted to get out of bed (dysania)
- Cystitis (inflammation of the urinary bladder), particularly interstitial cystitis in which urine cultures are negative
- Vision and eye problems, including sensitivity to light (photophobia), dry eyes, tunnel vision, night blindness, and difficulty focusing

An initial office examination may also find the following signs:

- Low blood pressure, particularly on standing (orthostatic hypotension)
- Low oral temperatures (less than 97°F)

- Slightly elevated oral temperatures (but less than 100°F) which are part of persistent flulike symptoms

- Increased heart rate (tachycardia)

- A positive Romberg test (unsteadiness when standing with eyes closed)

Novel and Conventional Laboratory Tests

Doctors usually perform the following laboratory tests, when attempting to diagnose a patient with CFS:

- Complete blood count (CBC) with differential
- Chem 20 panel
- Erythrocyte sedimentation rate (ESR), a marker of inflammation
- Urinalysis

Optional tests include:

- Antinuclear antibodies (ANA) and rheumatoid

factor (RF). (These are tests for rheumatoid arthritis and SLE, systemic lupus erythematous.)
- Thyroid tests (T3, T4, TSH)
- Adrenal tests (a.m. and p.m. cortisol levels)
- Lyme titers and HIV serology

Specific tests that support (but do not necessarily confirm) a diagnosis of chronic fatigue include (Verillo et al. 1997):

- Tests for viral infections, such as cytomegalovirus, Epstein-Barr virus, human herpes virus 6, and coxsackievirus
- Immune system tests, including low natural killer (NK) cell counts, elevated interferon alpha, tumor necrosis-alpha, interleukins 1 and 2, T-cell activation, altered T4/T8 cell ratios, low T-cell suppressor cell (T8) count, fluctuating B- and T-cell counts, antinuclear antibodies, immunoglobin deficiency, antithyroid antibodies
- Exercise testing may show decreased cortisol levels after exercise, decreased cerebral blood flow after exercise, inefficient glucose utilization, and erratic breathing patterns

Research into the cause(s) of CFS touches upon a vast array of systems and etiologies. Several laboratory tests, in addition to those mentioned above, may be helpful in guiding appropriate treatment. These would include:

- Functional assessments of the adrenal gland, including measurements of cortisol, DHEA (dehydroepiandrosterone), and DHEA-S
- Assessments of oxidative stress
- Homocysteine levels
- C-reactive protein, a sensitive marker of inflammation
- Toxin analysis, including heavy metals, pesticides, and organic chemicals

POSSIBLE CAUSES

Virus

Immune Response

Infection and Inflammation

Endocrine System

Chemical Sensitivity

Metal Sensitivity

Oxidative Stress

Side Effects

The causes of CFS are as yet undetermined, but studies have shown that multiple nutrient deficiencies, food intolerance, or extreme physical or mental stress may trigger chronic fatigue. Studies have also indicated that CFS may be activated by the immune system, various abnormalities of the hypothalamic-pituitary axes, or by the reactivation of certain infectious agents in the body. Some CFS patients were found to have low levels of PBMC beta-endorphin and other neurotransmitters. Thyroid deficiency may also be a contributing factor in CFS (refer to the Thyroid Deficiency protocol to find out how to determine if you are deficient in thyroid hormone production). A number of the triggers that may cause or exacerbate CFS are discussed below.

Virus and CFS

Symptoms of CFS resemble a postviral state and for this reason chronic viral conditions have been thought to contribute to CFS in some patients. Several viruses have been associated with CFS, including (Manian 1994):

- Herpes virus, particularly human herpes virus 6 (HHV-6)
- Epstein-Barr virus (a herpes virus which causes infectious mononucleosis)
- Cytomegalovirus (a herpes virus)
- Coxsackie viruses B1 and B4

If you are infected with a chronic, energy-depleting virus, there are conventional and alternative therapies that may be of help. It should be noted that most individuals have been exposed to pathogenic viruses that can be reactivated by adverse environmental conditions and cause chronic fatigue and other diseases.

Studies indicate that the Epstein-Barr virus may be suppressed with bilberry extract (anthocyanins), curcumin, carotenoids, and chlorophylls. The exact doses of these natural plant extracts that might be effective against Epstein-Barr have yet to be determined.

Immune Response to Bacterial and Viral Antigens

There are two different types of T-helper cells that

defend against different organisms:

T-helper 1 cells (Th1) target intracellular pathogens (organisms that invade cells) such as viruses. Interleukin-12 (IL-12) stimulates Th1 activation.

T-helper 2 cells (Th2) target organisms that are found outside of cells. Th2 cells are involved in humoral or antibody-mediated immunity and are triggered by interleukin-10 (IL-10), which is stimulated by bacteria, parasites, toxins, and allergens.

Each of the T-helper cells are activated by different cytokines. In a healthy condition, there is a balance between Th1 and Th2 activity. When presented with an acute infection, the Th1 system predominates (and Th2 is suppressed). In chronic infections, the Th2 system predominates, leading to antibody production.

Viruses, especially herpes viruses (such as Epstein-Barr virus, cytomegalovirus, and human herpes virus 6), make proteins that mimic IL-10, which activates the immune system and remains untouched by the body's natural defenses.

Addressing the two different types of T-helper cells has been the focus of work by Paul Cheney, M.D. His protocols are designed to stimulate Th1 and inhibit Th2.

According to Dr. Cheney, chronic fatigue patients have activation of T-helper 2 cells (Th2). Th2 activation suppresses T-helper 1 (Th1) activity, particularly cytotoxic T-cells and natural killer (NK) cells, which are the main defense against viruses. In this way the viruses are able to "fool" the immune system.

Several mechanisms can be used to stop the process of Th2 activation:

- Enhance natural killer (NK) cell function.
- Lower interleukin-10 (IL-10) levels, which will reduce Th2 activation.
- Raise interleukin-12 (IL-12) levels, which stimulate Th1 activation.

An article in the *Journal of Clinical Infectious Disease* measured NK cell activity in 50 healthy individuals and 20 patients with clinically defined chronic fatigue immune dysfunction syndrome (CFIDS). The patients were divided into three groups based on severity of clinical status. NK cell activity decreased

with the increasing severity of the clinical condition (Ojo-Amaize et al. 1994).

Several nutritional supplements, including essential fatty acids, vitamin A, vitamin E, DHEA, and melatonin, have been found to have beneficial effects on the Th1:Th2 ratio (see the Natural Therapies section).

For more specific information on the immune system, please refer to the Immune Enhancement protocol.

Chronic Fatigue Syndrome

Infection and Inflammation

A theory was published by Dr. Martin L. Pall, a professor of biochemistry and basic medical sciences at Washington State University, in 2001. The theory starts with the observation that infections that precede and may therefore induce CFS and related conditions act to induce excessive production of inflammatory cytokines. This initial step activates a series of reactions:

Inflammatory cytokines induce, in turn, nitric oxide synthase (iNOS), which synthesizes excessive amounts of nitric oxide.
Nitric oxide reacts with superoxide to produce the potent oxidant peroxynitrite.

Peroxynitrite acts via six known biochemical mechanisms to increase the levels of both nitric oxide and superoxide, which react to produce more peroxynitrite.

In this way, once peroxynitrite levels are elevated, they may act to continue the elevation, thus producing a self-sustaining vicious cycle. According to the theory, it is this cycle that maintains the chronic symptoms of CFS, and it is this cycle, therefore, that must be interrupted to effectively treat this condition (Pall 2001a).

Breaking the chain of inflammation caused by chronic viral infections would require a three-part protocol:

First, the underlying viral infection should be addressed with antiviral supplements (such as ginseng, echinacea, and lactoferrin) and those that shift the Th1:Th2 ratio (such as essential fatty acids and vitamin E).

Second, inflammation should be reduced with anti-inflammatory agents (such as essential fatty acids and curcumin).

Third, the nitric oxide system should be supported with supplements (such as arginine, vitamin B2 [riboflavin], vitamin B3 [niacin], and folate).

Role of the Endocrine System

Reduced Cortisol Levels

The HPA axis refers to the hypothalamus, pituitary, and adrenal glands, which are part of the endocrine system. The hypothalamus secretes several hormones that control the pituitary gland. The pituitary gland is considered the "master gland" of the endocrine system because it secretes hormones that control other glands (including the ovaries, testes, adrenals, and thyroid glands).

The hypothalamus stimulates the production of corticotropin, which stimulates the production of cortisol from the adrenal glands. "Many experts now think that chronic fatigue syndrome may be an example of the hypothalamus failing to properly regulate the brain's influence on the immune system," says Jay Lombard, M.D., assistant clinical professor of neurology at Weill Medical College of Cornell University in New York City and co-author of The Brain Wellness Plan (Neeck et al. 2000).

Researchers are exploring the relationship between cortisol and central neurotransmitter function, in particular, the relationship between cortisol and 5-HT (serotonin).

A review of the CFS database at King's College (London) found that one-third of the studies that reported baseline cortisol found it to be significantly low, usually in a third of patients. Methodological differences may account for some of the varying results. More consistent is the finding of reduced HPA function and enhanced serotonin (5-HT) function on neuroendocrine challenge tests (Parker et al. 2001).

A major role of the HPA axis is to restrain the immune system and prevent tissue damage. Reciprocal interactions between the HPA axis and immune system constitute a new endocrine feedback loop that has given rise to the field of neuroendocrine immunology (Torpy et al. 1996).

An article in the *Journal of Affective Disorders*

described a study in which cortisol levels were measured in 10 patients with CFS, 15 patients with major depression, and 25 healthy controls. Baseline circulating cortisol levels were highest in the depressed patients; lowest in the CFS patients; and intermediate between the two in the control group of 25 healthy individuals. Prolactin responses to the selective serotonin-releasing agent d-fenfluramine were lowest in the depressed patients, highest in the CFS patients, and intermediate between both in the healthy group. The authors concluded that depression is associated with hypercortisolemia and reduced central serotonin neurotransmission and suggest that CFS may be associated with hypocortisolemia and increased 5-HT function (Cleare et al. 1995).

Addison's disease results from hyposecretion of cortisol and is characterized by weakness, fatigue, and dizziness upon standing. As described below, CFS may be a mild form of Addison's disease. Blood tests can determine serum cortisol levels. Blood must be drawn in the morning and afternoon because cortisol levels are higher during the day and lower at night. Total normal cortisol levels (morning and evening) in adults are:

8 a.m.: 5-23 mcg/dL (138-635 nmol/L)

4 p.m.: 3-16 mcg/dL (83-441 nmol/L)

8 p.m.: less than 50% of 8 a.m. levels

Adrenal Fatigue

As noted, it has been proposed that CFS is a mild form of Addison's disease (referred to as adrenal insufficiency or hypoadrenalism). The following evidence has been presented (Jefferies 1994; Baschetti 1999; Jeffcoate 1999; Baschetti 2000):

Many of the symptoms of CFS overlap those of Addison's disease (adrenal failure).

Improvement in CFS patients has occurred after supplementation with mineralocorticoids (fludrocortisone), low-dose hydrocortisone (cortisol), and licorice (an old herbal remedy for Addison's disease).

Multiple Chemical Sensitivity

Multiple chemical sensitivity (MCS) is a controversial term. Synonyms for MCS are twentieth century disease, Environmental Illness, Total Allergy

syndrome, Chemical AIDS, and Idiopathic Environmental Illness. It is believed by some that exposure to a chemical (or many chemicals) can trigger a complex of symptoms called MCS. It appears to affect young women at a higher rate than men. There has not been a consensus on the specific definition for MCS. The disorder is characterized by recurring symptoms affecting multiple organ systems.

The individual demonstrates symptoms of MCS when exposed to many unrelated chemicals, in doses that are far below those recognized to cause harm in the general population. No single, widely accepted test of physiologic function can be correlated with the symptoms (Cullen 1987a; 1987b).

The theories for MCS include, but are not limited to, dysfunction of the immune system and neurological abnormalities--specifically, chemical sensitization of the limbic system--and various psychological theories. To date, no studies have validated any theory. One study points out that MCS, fibromyalgia, CFS, and post-traumatic stress disorder are overlapping diseases, sharing common symptoms. Very often, each disorder seems to be induced by a relatively short-term stress, which is followed by a chronic pathology, suggesting that the stress may act by inducing a self-perpetuating vicious cycle.

Pall et al. (2001b) believe that the vicious cycle mechanism is the explanation for the etiology of CFS and MCS, based on the elevated levels of nitric oxide and its potent oxidant product, peroxynitrite, found in both conditions.

Beckman et al. reported that peroxynitrite reacts with and inactivates several important mitochondrial enzymes leading to metabolic energy dysfunction (Beckman et al. 1993; Radi et al. 1994), characteristics of both CFS and MCS.

Metal Sensitivity

The effect of dental metal (amalgam) removal was studied in 111 patients with metal hypersensitivity and symptoms resembling CFS. After consultation with a dentist, the patients decided to replace their metal restorations with nonmetallic materials. A significant number of patients had metal-specific lymphocytes in the blood. Nickel was the most common, followed by inorganic mercury, gold, phenyl-mercury, cadmium, and palladium.

As compared to lymphocyte responses in healthy subjects, the CFS group had significantly increased responses to several metals, especially to inorganic mercury, phenyl-mercury, and gold. Following dental metal removal, 83 patients (76%) reported long-term health improvement; 24 patients (22%) reported unchanged health; and two patients (2%) reported worsening of symptoms. Following dental metal replacement, the lymphocyte reactivity to metals decreased as well (Stejskal et al. 1999) (see "Mercury Amalgam Toxicity" in the May 2001 issue of Life Extension Magazine).

Oxidative Stress

Studies have shown that oxidative stress plays a role in the development of CFS (Fulle et al. 2000; Richards et al. 2000; Logan et al. 2001). Oxidative stress is a term used to describe the body's prolonged exposure to oxidative factors that cause more free radicals than the body can neutralize. Free radicals are produced as a byproduct of normal metabolic functions. When there are enough free radical scavengers present, such as glutathione and vitamins C, E, and A, along with zinc and other nutrients, through normal metabolic functioning, the body will "mop up" or neutralize the free radicals. When free radicals are not neutralized, the body can become vulnerable to cellular destruction.

A relationship between abnormal oxidative stress and CFS can be found in the literature. An article in the journal Life Science described a study that showed that patients with CFS had lower serum transferrin levels and higher lipoprotein peroxidation. These results indicate that patients with CFS have increased susceptibility of LDL and VLDL to copper-induced peroxidation and that this is related both to their lower levels of serum transferrin and to other unidentified pro-oxidizing effects of CFS (Manuel y Keenoy et al. 2001).

Exercise has been shown to increase the production of oxidants. Fortunately, regular endurance exercise results in adaptations in the skeletal muscle antioxidant capacity, which protects myocytes (muscle cells) against the deleterious effects of oxidants and prevents extensive cellular damage (McCully et al. 1996; Powers et al. 1999).

A study of the oxygen delivery to muscles in patients with CFS found that oxygen delivery and oxidative metabolism was significantly reduced in CFS patients after exercise (compared with sedentary controls)

(McCully et al. 1999).

Possible Related Side Effects of CFS:

Orthostatic Hypotension

Orthostatic hypotension is defined as an excessive fall in blood pressure on standing, usually greater than 20/10 mmHg. It is considered to be a manifestation of abnormal blood pressure regulation due to a variety of causes.

Hypotension, particularly orthostatic hypotension, is a common symptom in chronic fatigue patients. Many people with CFS have chronic low blood pressure (the normal is 120/80 mmHg), which is made even worse on standing. This may be a particular problem in the morning, when standing can cause dizziness. Exercise or a heavy meal may exacerbate the symptoms. Syncope is a loss of consciousness and postural tone caused by diminished cerebral blood flow. Syncope often occurs during the morning shower, perhaps due to the vasodilating effect of hot water.

There are several mechanisms that govern blood pressure. Upon standing, a large amount of blood pools in the veins of the legs and trunk. The transient decrease in venous return to the heart results in a low blood pressure. The body responds with a sympathetic-mediated release of catacholamines that increase heart rate contraction and vasoconstrict the arteries. With continued standing, antidiuretic hormone (ADH) is secreted which activates the renin-angiotensin-aldosterone system, subsequently causing sodium and water retention and an expansion of the circulating blood volume.

There are many causes of orthostatic hypotension, including:

Hypovolemia (low blood volume) induced by excessive use of diuretic agents (e.g., loop diuretics, such as furosemide, bumetanide, and ethacrynic acid) and relative hypovolemia due to vasodilator therapy with nitrate preparations and calcium antagonists (verapamil, nifedipine, or diltiazem) or with angiotensin converting enzyme (ACE) inhibitors.

Histamine, a key player in allergic reactions, induces vasodilation and hypotension.

Potassium deficiency (hypokalemia) impairs the reactivity of vascular smooth muscle and may limit the increase in peripheral vascular resistance on standing.

The adrenocortical hypofunction of Addison's disease may lead to orthostatic hypotension in the absence of adequate salt intake.
Several classes of drugs reversibly impair autonomic reflexes and reduce blood pressure on standing as an important adverse effect.

These include many drugs used to treat psychiatric disorders such as the monoamine oxidase inhibitors (MAOIs) (isocarboxazid, phenelzine, and tranylcypromine) used to treat depression; the tricyclic antidepressants (nortriptyline, amitriptyline, desipramine, imipramine, and protriptyline) or tetracyclic antidepressants; and the phenothiazine antipsychotic drugs (chlorpromazine, promazine, and thioridazine). Other drugs that may produce orthostatic hypotension are quinidine, L-dopa, barbiturates, and alcohol.

Elevated Homocysteine Levels

Homocysteine is a sulfur-containing amino acid that is produced as a byproduct of methionine metabolism. When the body has an adequate supply of cofactors, such as vitamins B6, B12, and folic acid, homocysteine is detoxified, rendering compounds useful for other functions. Currently, homocysteine levels are in the forefront as a cardiovascular risk because of the damage that can occur to blood vessels and arteries when homocysteine levels are high.

A study of 12 women who fulfilled the criteria for both fibromyalgia and CFS found that, in all the patients, the homocysteine levels were increased in the cerebrospinal fluid (CSF). There was a significant positive correlation between CSF homocysteine and B12 levels and fatigue-ability, as rated on the Comprehensive Psychopathological Rating Scale. The authors concluded that "increased homocysteine levels in the central nervous system characterize patients fulfilling the criteria for both fibromyalgia and chronic fatigue syndrome."

They also noted that B12 deficiency caused a deficient remethylation of homocysteine. Therefore, a vitamin B12 deficiency can be considered a contributing factor to the higher homocysteine elevations found in these patient groups (Regland et al. 1997).

Glutathione Deficiency

Glutathione is a tripeptide made up of three amino acids: glycine, cysteine, and gamma-glutamic acid. Glutathione functions as a modulator of cellular homeostasis, including detoxification of oxyradicals and metals. It also acts as a potent free radical scavenger that can help prevent damage to DNA and RNA, detoxify heavy metals, boost immune function, and assist the liver in detoxification through its various enzymes. Levels of intracellular glutathione decrease with age, lowering the body's ability to detoxify free radicals and the many important enzymes glutathione makes.

An article in the journal *Medical Hypothesis* proposed that glutathione, an antioxidant essential for lymphocyte function, may be depleted in CFS patients. Glutathione is needed for both the immune system and for aerobic muscular contraction. The authors proposed that glutathione depletion by an activated immune system also causes the muscular fatigue and myalgia associated with CFS (Bounous et al. 1999).

Cysteine is a precursor to glutathione. It has been hypothesized that glutathione and cysteine metabolism may play a role in skeletal muscle wasting and muscle fatigue. The combination of abnormally low plasma cysteine and glutathione levels, low natural killer (NK) cell activity (with a resulting susceptibility to viral infection), skeletal muscle wasting or muscle fatigue, and increased rates of urea production define a complex of abnormalities that is tentatively called "low CG syndrome." These symptoms are found in patients with HIV infection, cancer, major injuries, sepsis, Crohn's disease, ulcerative colitis, CFS, and to some extent in overtrained athletes (Droge et al. 1997).

The CFS Case Definition

The EBV work sparked new interest in the syndrome among a small group of medical researchers. They realized they needed a standard way to describe CFS so that they could more easily compare research results.

In the late 1980s, CDC brought together a group of CFS experts to tackle this problem. Based on the best information available at the time, this group published in the March 1988 issue of the scientific journal, Annals of Internal Medicine, strict symptom and physical criteria -- the first case definition -- by

which scientists could evaluate CFS study patients.

Not knowing the cause or a specific sign for the disease, the group agreed to call the illness "chronic fatigue syndrome" after its primary symptom. "Syndrome" means a group of symptoms that occur together but can result from different causes. (Today, CFS also is known as myalgic encephalomyelitis, postviral fatigue syndrome, and chronic fatigue and immune dysfunction syndrome.)

After using this definition for several years, CFS researchers realized some criteria were unclear or redundant. An international group of CFS experts reviewed the criteria for CDC, which led to the first changes in the case definition. This new definition was published in the same journal in December 1994.

Besides revising the CFS case criteria -- which reduced the required minimum number of symptoms to four out of a list of eight possible symptoms -- the newer report also proposed a conceptual outline for studying the syndrome. This outline recognizes CFS as part of a range of illnesses that have fatigue as a major symptom. Although primarily intended for researchers, these guidelines should help doctors better diagnose CFS.

For most people, CFS symptoms plateau early in the course of illness and thereafter wax and wane. Some people get better completely, but it is not clear how frequently this happens. Emotional support and counseling can help you and your loved ones cope with the uncertain outlook and the ups and downs of this illness.

Conclusion

CFS seems to involve interactions between the immune and central nervous systems, interactions about which scientists know relatively little. Scientists' concerted efforts to penetrate the complex nervous system and immune system events in CFS have created a challenging new concept of the pathology of this and other illnesses.

Source: The National Institute of Allergies and Infectious Diseases (online at http://www.niaid.nih.gov/factsheets/cfs.htm). Dated January 2001. Additional source: The sections titled "Diagnostic Criteria" and "Possible Causes" are from the Life Extension Foundation (LEF), updated in March 2003.

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